Memorandum:

DRAFT

To File: BLA 99-0128

From: Lauren E. Black, Ph.D., Reviewing Pharmacologist

Through: M. David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch

Through: Karen Weiss, M.D., Director, Division of Clinical Trials Design and Analysis

Subject: Pharmacology Review of the infliximab BLA

Product: Remicade®, Infliximab (cA2), chimeric (human/murine) IgG1 for use in Rheumatoid Arthritis

Sponsor: Centocor, Inc.

Date: 10/28/99

BACKGROUND: Infliximab has very limited crossreactiivity and binds only to human and chimpanzee TNFa. The sponsor has produced a highly analogous mouse-rat chimeric antibody directed at mouse TNFa which is designated cV1 q by replacing the rat heavy and light chain constant domains with those from a mouse IgG2a antibody. Prior to initiating multiple dose toxicity studies (i.e. fertility and general reproduction and 6-month chronic studies) with cV1q in mice, a pharmacokinetic and tolerance study was conducted to assure that at least 3 months of once weekly intravenous dosing would be tolerated and that high cV1 q serum levels could be maintained (see review below). Dosing was consistent with pharmacologically active doses and schedules utilized in murine activity models. Development of mouse anti-chimeric antibodies (MACA) were evaluated; cV1q proved to be sufficiently nonimmunogenic in mice such that long term studies are feasible and pharmacologically relevant to assessing risk of the human drug.

INTRODUCTION: This is the — BLA for infliximab. There are two toxicology issues new to this file. The first issue is the chronic dosing regimen proposed for the RA indication, necessitating the conduct of a new chronic toxicology study. This decision is in keeping with two ICH documents, M3 and S6, pertaining to clinical risk assessment of drugs and biologic therapies. CV1 q is currently being dosed in mice for 6 months. While the starting date for the chronic toxicology study was originally intended to provide draft toxicology data to the BLA during its review period at FDA, the study start was delayed due to a production setback. Since cV1q is analogous and non-identical to the human product, we have agreed with the sponsor that the study could be completed and reported post approval. Study results are expected for submission to FDA in the year 2000. Based on the broader clinical population treated with infliximab, it was desirable from a public health perspective to evaluate the effects of infliximab on additional reproductive endpoints. The sponsor evaluated cV1 q in mice in a study of male and female fertility and general reproductive performance (see review below).

REGULATORY CONCLUSIONS: These studies (completed and in progress) are adequate to support the proposed labeling for the current clinical indication. No changes to the sponsor's proposed wording are required. See Dr. Matthew's review regarding clinical issues.

CONCLUSIONS: Based on review of the pharmacology and toxicology data, the safety of infliximab is adequately supported, and no objection is offered to approving this licensing application. The review is provided as an attachment to this cover sheet.

REVIEWER.: _____

Lauren E. Black, Ph.D., Reviewing Pharmacologist, DCTDA, CBER

CONCURRENCE: Martin D. Green

Martin David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch, DCTDA, CBER

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B. Matthews, M.D., HFM-582; K. Brorson, Ph.D., HFM-561; M. Noska, HFM-588

ATTACHMENT

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PHARMACOLOGY AND TOXICOLOGY SYNOPSIS BLA (98-0012) FOR CROHN'S DISEASE:
Tissue Crossreactivity: Chimeric A2 (cA2) showed no unexpected reactivity (or cross-reactivity) in *in vitro* human tissue cross-reactivity assessment, nor mutagenicity, local intolerance, reproductive, or other systemic toxicities that would preclude its use in Crohn's Disease patients.

Pharmacology: The following pharmacologic properties can be attributed to cA2:

- cA2 binds to TNFα homotrimer with high affinity (Ka = 10^{10} M^{-1}); it specifically neutralizes TNFα and does not neutralize lymphotoxin.
- cA2 also binds to both the monomeric subunits of TNFα and transmembrane TNFα; after cA2 binds to cells expressing transmembrane TNFα they can be lysed by the addition of complement or effector cells.
- The stable complex formed between TNFα and cA2 is responsible for blocking TNFα activity.

Safety Studies in Chimpanzees with cA2: The chimpanzee is the only species other than humans whose TNFα binds to cA2, therefore safety studies in this species are considered the only preclinical studies that can provide direct safety information on cA2 administration to humans. However, due to animal use restrictions on this endangered species, these animals may not be necropsied to provide histopathology data, and therefore study outcomes are limited to clinically observable signs as well well as results from noninvasive testing (such as clinical chemistry and hematology assessments). Following some problems attibutable to high doses of ketamine anesthetic required for animal handling, the studies with cA2 in chimpanzees showed that cA2 was well tolerated at doses up to 30 mg/kg/day for at least 3 consecutive days and at doses up to 15 mg/kg/day for at least 5 days. No cA2-related signs of toxicity, including abnormal hepatic or hematologic effects, were observed during these chimpanzee studies. cA2 has a long serum half-life (6 days in chimpanzees) and predictable pharmacokinetics.

Mouse Studies with Analogous Antibody: Doses of cV1q, an analogous anti-mouse TNFα monoclonal antibody which were active in a mouse model of disease, when given to pregnant mice during organogenesis, caused no embryofetal toxicities. These studies were necessitated due to the absence of crossreactivity of cA2 in species other than chimpanzees.

NEW STUDIES.

CHRONIC PHARMACOKINETICS:
12-Week Intravenous Dose Pharmacokinetic and Tolerance Study of cV1q Anti-Mouse TNFa Antibody in CD-1® Mice (Centocor Study P-098-018)
The purpose of this study was to evaluate the pharmacokinetics and potential toxicity of cV1q in mice when administered intravenously once weekly for 12 consecutive weeks. Based on the results of this study, the feasibility of conducting multiple dosing toxicity and/or pharmacology studies with cV1q was determined.

Ten male CD-1® mice were obtained from (——————— The mice were assigned to two treatment groups (5 mice/group). cV1q (Lots _____ and _____ 5 mg/mL) was administered at a dose of 10 or 40 mg/kg at a dose volume of 10 mL/kg. Chimeric V1q was administered intravenously (bolus dose) into the caudal vein once weekly for 12 consecutive weeks. Clinical signs were recorded daily. Body weights were recorded predose and just prior to each weekly dose. Serum samples were collected from all study mice one day prior to weekly doses 1, 2, 4, 8, 10 and 12, and at week 13 for determination of serum cV1q concentration. Alanine transaminoferase (ALT) was evaluated in serum samples collected at study week 13. Other serum chemistry parameters were not evaluated because of the limited sera available for testing. All study mice were euthanized and submitted to necropsy at 13 weeks (7 days after the 12th dose). Brain, adrenal gland, lung, liver, spleen, kidney, urinary bladder, heart, mesenteric lymph node, colon and small intestine were collected and fixed in 10% buffered formalin. Histopathologic examination was performed by light microscopy on hematoxylin/eosin stained tissues/organs.

No mortality or signs of toxicity were observed during the study in CD-1® mice administered 12 weekly intravenous doses (10 or 40 mg/kg/dose) of cV1q. No changes considered to be cV1q treatment-related were observed for body weight, ALT or histopathologic evaluations. Serum cV1q concentration analyses revealed that weekly intravenous doses of cV1q at 10 and 40 produced high serum cV1q concentrations. Serum cV1q concentrations for the 10 mg/kg dose group reached a steady state after 9 weekly doses (» 200 mg/mL). Serum cV1q concentrations for the 40 mg/kg dose group reached concentrations of approximately 800 mg/mL after 7 doses, but by the end of the study the serum concentrations were lower (» 400-500 mg/mL).

Thus, cV1q was well tolerated in CD-1® mice following 12 weekly intravenous doses of 10 or 40 mg/kg. Serum cV1q concentration analyses revealed that high serum concentrations of cV1q were achieved and maintained during the study.

REPRODUCTIVE TOXICITY

Intravenous Fertility and General Reproduction Toxicity Study of cV1q Anti-Mouse TNFa Antibody in CD-1® Mice (Centocor Study T-098-003)

The purpose of this study was to evaluate the potential toxic effects of cV1q on fertility and general reproduction in male and female mice. This study was designed to evaluate ICH Harmonized Tripartite Guideline stages A and B of the reproductive process. This included detection of potential effects on the estrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryos of female mice and permit detection of functional effects (e.g., effects on libido or epididymal sperm maturation) that may not be detected by histological examinations of male mouse reproductive organs.

Seventy-five male and 75 female CD-1® mice, obtained from (——————————— were randomly assigned to three dose groups (25/sex/dose group). Prior to randomization the females were evaluated for evidence of normal estrous cycling. The three dose groups were administered intravenously (bolus dose) into the caudal vein with either control vehicle (1X Dulbecco's Phosphate Buffered Saline) or cV1q (Lots ——— and ——— 0.5 mg/mL and 2.0 mg/mL). cV1q was administered at dosages of 10 and 40 mg/kg/dose. Both cV1q and control vehicle were administered at a dose volume of 20 mL/kg.

Male mice were administered cV1q or control vehicle once weekly beginning 56 days (8 weeks) before cohabitation and continuing through cohabitation (2 weeks) and the week before sacrifice. Female mice were administered cV1q or control vehicle once weekly beginning 2 weeks before cohabitation (maximum of 14 days) and on day 0 and day 7 of gestation. All mice were observed once daily for clinical signs, except on dose days, when observations were recorded before injection and for approximately 60 minutes after injection. Body weights were measured weekly. In addition, the female mice were weighed daily during the gestation period. Blood samples were collected from all surviving male and female mice just prior to necropsy for cV1q serum concentration analyses. Female mice were Caesarian-sectioned on day 11 of gestation and the thoracic, abdominal and pelvic viscera grossly examined and gross lesions collected in neutral buffered formalin. The number of corpora lutea in each ovary was recorded. The uterus was excised and examined for pregnancy, number and distribution of implantations and viable and nonviable embryos. The ovaries were collected in neutral buffered formalin for possible future evaluation. Male mice were sacrificed after completion of the cohabitation period and the thoracic, abdominal and pelvic viscera were grossly examined and gross lesions collected in neutral buffered formalin.

The following male organs were individually weighed and collected in neutral buffered formalin (the testes were fixed in Bouin's solution for 48 to 96 hours before being placed in formalin): right testis, left testis, left epididymis, right epididymis, seminal vesicles and prostate. Sperm concentration and motility were evaluated.

Several male and female animals died during the study. Male mortalities included one mouse in the 0 (vehicle control) and 10 mg/kg dosage groups and two mice in the 40 mg/kg dosage group. Female mortalities included four mice in the 10 mg/kg dosage group and three mice in the 40 mg/kg dosage group. No gross findings related to cV1q treatment were observed at necropsy and the exact causes of

death were not determined. However, it is possible that the deaths for the cV1q-treated animals were related to hypersensitivity reactions to multiple cV1q doses since most of the deaths occurred on the day of dosing following 3 to 6 weekly doses. No signs of toxicity or body weight changes considered cV1q-related were observed during the study in either male or female treated mice. Estrous cycling was unaffected by cV1q treatment. All mating and fertility parameters [fertility and pregnancy indicies (number of pregnancies per number of mice in cohabitation and mice that mated, respectively), number of days to inseminate, number of mice that mated and number of mice with confirmed mating dates during the first and second week of cohabitation] were unaffected by cV1q treatment. Only one mouse failed to have a confirmed date of mating. Pregnancy occurred in 23 (92%), 21 (91%) and 19 (76%) of the female mice in the 0 (vehicle control), 10 and 40 mg/kg dosage groups, respectively. The slightly lowered pregnancy rate in the 40 mg/kg dosage group was not considered related to cV1q treatment, because the pregnancy rate was only slightly lower than the historical control range (83-100%) for the Test Facility ('[redacted]') and there was no effect on fertility parameters evaluated at Caesarean-sectioning.

No litter parameters were affected by cV1q. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weights, percent resorbed conceptuses, and percent live male fetuses were comparable among the cV1q and vehicle control treatment groups and did not significantly differ. No dam had a litter consisting of only resorbed conceptuses, and there were no dead fetuses. No cV1q-related necropsy findings were observed in male or female animals. No organ weight changes considered cV1q-related were observed in the male animals. The number of motile sperm, motile percent, nonmotile and total and sperm count were unaffected by cV1q treatment. Serum cV1q concentration analyses from samples collected just prior to necropsy showed that weekly doses of cV1q at 10 and 40 mg/kg produced significant cV1q serum concentrations in both male and female animals, which verified cV1q exposure during the study.

Thus, cV1q at weekly dosages of 10 and 40 mg/kg in male and female CD-1® mice produced no toxic effects on fertility and general reproduction in male and female mice. **The new wording for the Remicade label as currently proposed by the sponsor (10/28/99) is as follows: "No impairment of fertility was observed in a fertility and general reproduction toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFa." This is an adequate description of the results.**

DESIGN FOR THE CHRONIC INTRAVENOUS DOSE TOXICITY STUDY (IN PROGRESS)

1) 6-Month Chronic Toxicity Study of cV1q muG2a Anti-Mouse TNFa Antibody in CD-1® Mice (Centocor Study T-098-004) The purpose of this study is to evaluate the potential toxicity of cV1q, anti-mouse TNFa monoclonal antibody, in CD-1® mice when administered intravenously once weekly for six months. In this 6-month chronic toxicity study, 240 CD-1® mice (120 male and 120 female) will be obtained from [redacted] and assigned to dose groups shown in Table 3.

Table 1 Study design for study T-098-004

Dose Group	Dose	Number of Mice Submitted to Necropsy							
		Initiated		3 Months		6 Months		Recovery	
		M	F	M	F	M	F	M	F
Control	0	40	40	10	10	20	20	10	10
cV1q	10	40	40	10	10	20	20	10	10
cV1q	40	40	40	10	10	20	20	10	10

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